EDITORIAL COMMENT

Antioxidant Vitamins: Sorting Out the Good and the Not So Good*

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Once upon a time, free radical biology was studied primarily by physical chemists who minded their electrons in relative obscurity. That their interests might one day be shared by clinical cardiologists would have seemed most unlikely. Yet today, many cardiologists—confused by seemingly contradictory clinical reports, egged on by curious patients and aggravated by overstated media reports and the billion-dollar over-the-counter vitamin industry—may wish they had paid more attention to oxygen metabolism during their biochemistry lectures. The word on the street, and in the waiting room, is that antioxidants—in particular, antioxidant vitamins—are sexy, profitable and as wholesome as mother’s milk. Given this popular impression, why have careful cardiologists not yet recommended their use on a broader scale for the treatment or prevention of cardiovascular disease? Simply put, although the scientific rationale, epidemiologic data and retrospective studies are very convincing, the data from prospective, randomized trials have failed to show a consistent benefit. To resolve these contradictions, we need a better understanding of the differences among the various antioxidant vitamins, the means by which these antioxidants exert their effects and whether all or some subset of individuals will benefit from the use of antioxidant vitamins.

Vitamin E: clinical data. Vitamin E has been of particular interest in recent years, and the mixed data on its use (reviewed in [1]) are illustrative in considering the potential influence of the study published in this issue of the Journal by Saldeen et al. (2). Previously, two prominent, well-designed epidemiologic studies linked high vitamin E consumption with a favorable cardiovascular risk profile (3,4), yet close correlations between serum vitamin E levels and improved cardiovascular outcomes have not always been found (5,6). Randomized, prospective clinical trials of vitamin supplementation have been even more confusing. Treatment with beta-carotene, a precursor of vitamin A, was linked to an increased risk of ischemic heart disease in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (7). For vitamin E, the efficacy demonstrated in prospective clinical trials has been more promising, but still inconclusive (Table 1). In the Cambridge Heart Antioxidant Study (CHAOS), patients randomized to vitamin E supplementation had a significant reduction in the risk of nonfatal myocardial infarction, but an increase in all-cause mortality (8). To make matters more confusing, data from the Gruppo Italiano per lo Studio della Streptochinasi nell’Infarto miocardico (GISSI) prevention study, reported at the 48th Annual American College of Cardiology Sessions in March 1999 (not yet published), do not demonstrate a beneficial effect of vitamin E on major cardiovascular end points. These studies alone are enough to explain the bewilderment of clinical cardiologists seeking to rationalize the data regarding antioxidant vitamin prescription.

Sources of oxidative stress. For those attempting to make sense of the rather ambiguous human studies addressing the role of antioxidant vitamins in cardiovascular risk reduction, it may be prudent to consider the sources of the reactive oxygen species (ROS) that they combat, and the effects these ROS have on the cardiovascular system. Diet and environmental factors such as cigarette smoking are important direct and indirect sources of oxidative stress (9,10), which may in part explain their atherogenic effects. However, endogenous sources of ROS are at least of equal importance. Cells within blood vessels generate ROS, including endothelial and smooth muscle cells (11,12). Indeed, ROS may directly induce vascular smooth muscle cell proliferation (13) and are important mediators of the effects of proatherogenic factors such as platelet-derived growth factor (14). Our own laboratories have shown that thrombin, which has procoagulant, vasoconstricting and proliferative effects on vascular cells, potently stimulates ROS through a novel cellular oxidase system (15). Also, as shown in the study of Saldeen et al. (2), thrombosis itself is likely a potent initiator of ROS generation in the vasculature.

How do these endogenous ROS, which are predominantly short-lived species such as hydrogen peroxide and superoxide anion, result in the long-term changes associated with atherogenesis? One possibility is that lipids, proteins and deoxyribonucleic acid (DNA) are oxidatively modified by ROS, and that these modified proteins have long-lived and deleterious consequences to the vasculature. The oxidation of low density lipoprotein would be an excellent example of such a process (16). 4-Hydroxynonenal is an oxidatively modified fatty acid product with relatively long-lived effects that may have atherogenic properties (17).

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Oxidative modification of DNA, particularly within the mitochondrial genome, may also account for some of the long-term changes in cellular function that result in progression of atherosclerosis (unpublished data).

**Vascular effects of oxidative stress.** Increased levels of ROS, either from endogenous or exogenous sources, have pleiotropic effects on the vascular system. As mentioned earlier, they are potent stimuli for smooth muscle cell proliferation, which is an early event in vascular lesion formation. Reactive oxygen species such as superoxide anion also impair endothelium-dependent vasodilation (18), an effect that may be due at least in part to conversion of nitric oxide to peroxynitrite. Acting through a similar mechanism, ROS can promote platelet aggregation (19). Reactive oxygen species may affect the stability of atherosclerotic plaques through direct toxic effects on the vascular endothelium (20) by increasing the expression of macrophage-homing proteins such as vascular cell adhesion molecule-1 (21) and by activating macrophage-derived matrix metalloproteinases (22). Thus, ROS have the capability to affect virtually every step of the atherogenic injury process (23).

**Effects of alpha- and gamma-tocopherol on variables of thrombosis and oxidative stress.** If ROS influence so many proatherogenic pathways, how is it possible that clinical studies testing antioxidant vitamins have yielded no consistent answers for the physician? The present study by Saldeen et al. (2) demonstrates that orally administered vitamin E does indeed have considerable effects on endogenous variables of ROS metabolism, and it also has the ability to block platelet aggregation and thrombus formation in a rat FeCl₃-induced abdominal aorta thrombosis model. This study is remarkable not only for the close correlation made between clinically relevant end points (platelet aggregation and thrombosis) and multiple variables of endogenous ROS activity, but also for the differences noted when rats were fed equal amounts of the two bioavailable forms of vitamin E—alpha- and gamma-tocopherol. The investigators found that gamma-tocopherol was significantly more potent than alpha-tocopherol in inhibiting thrombosis and in eliciting a favorable profile of oxidative variables. These results are somewhat surprising and provide a lens through which the results of clinical trials described earlier might be viewed a bit more clearly.

To understand the study of Saldeen et al. (2), the biologic differences between alpha- and gamma-tocopherol should be considered. The two isoforms differ structurally by a single methyl group substitution. Alpha-tocopherol has more potent vitamin E activity than does gamma-tocopherol (24), is found in higher plasma concentrations (25) and may itself suppress gamma-tocopherol levels (26). Alpha-tocopherol is a more potent antioxidant in vitro than is gamma-tocopherol (27), yet gamma-tocopherol has a greater capacity to remove potent peroxynitrite-derived species such as nitric oxide (28). These differences are particularly relevant because although gamma-tocopherol is the most abundant form of vitamin E in the diet, oral vitamin E supplements are exclusively preparations of alpha-tocopherol (29). Although the nuances of these vitamin E isoforms are relatively underappreciated, they provide a potential explanation for why vitamin E supplementation does not confer the same benefit as high dietary intake of vitamin E.

If these experiments can be replicated in other models and with other experimental end points, we will be forced to ask whether the clinical studies of vitamin E supplementation using alpha-tocopherol have been misguided. There are few clinical data to bear on this question; however, it is interesting to note that only serum levels of gamma-tocopherol, and not alpha-tocopherol, are reduced in patients with coronary artery disease (30). It is quite conceivable that vitamin E supplementation for the prevention of cardiovascular disease might involve a careful prescription not only of particular isoforms of the vitamin, but also of precise dosages. This is in contrast to the “megadose” mentality often displayed by vitamin-gobblers, and would take considerable education of physicians and their patients to implement. The experiments of Saldeen et al. (2) also indicate that a much better fundamental understanding of the cellular and physiologic effects of antioxidant vitamins is needed to guide the clinical trials that will help us to decide which dietary supplements are good and which are not so good, from a cardiovascular perspective.

**Measures of oxidative stress.** To compound these difficulties, there remains no good method to determine which individuals are most likely to benefit from antioxidant therapies. Imagine the likelihood of determining the efficacy

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**Table 1.** Large, Randomized Trials of Vitamin E Supplementation (i.e., Alpha-Tocopherol) in Patients With Coronary Artery Disease

<table>
<thead>
<tr>
<th>Study (reference)</th>
<th>Criteria for Enrollment</th>
<th>n</th>
<th>Length of Follow-Up</th>
<th>Dose</th>
<th>Effect of Alpha-Tocopherol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapola et al. (7)</td>
<td>Male smokers with previous MI</td>
<td>1,862</td>
<td>5.3 years</td>
<td>50 mg/day</td>
<td>Significant reduction in nonfatal MI; nonsignificant increase in CV mortality and all-cause mortality</td>
</tr>
<tr>
<td>CHAOS (8)</td>
<td>Angiographically proved CAD</td>
<td>2,002</td>
<td>510 days</td>
<td>800 IU/day for first 546 patients then 400 IU/day</td>
<td>No difference in MI or mortality</td>
</tr>
</tbody>
</table>

CAD = coronary artery disease; CHAOS = Cambridge Heart Antioxidant Study; CV = cardiovascular; MI = myocardial infarction.
of an antihypertensive medication if it was applied to the population in general, or of using cholesterol-lowering medications indiscriminately without knowledge of serum cholesterol values. There are hints that it may be possible to develop such a marker (or group of markers); the measurement of F2-isoprostanes (31) and a newly reported method for measuring mitochondrial DNA damage (32) appear promising but preliminary.

Conclusions. The usefulness of antioxidants for the prevention of cardiovascular diseases has yet to be definitively proven. However, studies such as those of Saldeen et al. (2) offer important potential insights that, together with the development of methods to identify individuals most likely to benefit, provide hope to clinicians seeking to use antioxidant vitamins with safety and efficacy for the treatment and prevention of cardiovascular disease.

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REFERENCES


